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Effect of *Artocarpus heterophyllus* Lam. (Jackfruit) on Indomethacin-Induced ulcer model in albino rats

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ABSTRACT

The objective of present study is to investigate anti-ulcer activity of Artocarpus heterophyllus Lam. leaves extracts on indomethacin induced ulcers in rats and establish the probable mechanism of antiulcer activity, if any and confirm the validity of claims of the activity as mentioned in texts as traditional medicines. The leaves were extracted with methanol and anti-ulcer activity was evaluated for effects on indomethacin-induced gastric ulceration on Swiss albino rats. The various parameter used to assess anti-ulcer activity were pH of gastric contents, concentration of acid in gastric contents and gastric ulcer scoring in indomethacin- induced ulcer model. The methanolic extract (500 mg/kg, p.o.) exhibited inhibition of indomethacin-induced gastric ulceration, decreasing concentration of acid in gastric content and increasing pH of gastric contents. Acute toxicity study showed that there was no mortality after the application of extract in doses above 5000mg/kg. The anti-ulcer property probably acts via a reduction in gastric acid secretion.

Keywords: Anti-ulcer, *Artocarpus heterophyllus* Lam., Indomethacin, Ulcer, Gastric acid secretion

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INTRODUCTION

From time immemorial, medicinal plants have been used for the treatment of many debilitating health ailments of man. These are often used as herbal remedies which could be herbs or herbal materials, herbal preparations and finished herbal products containing as active ingredients plants parts, plant materials or their combinations in various proportions. They are mostly used as herbal teas, decoctions or extracts with easily accessible and affordable liquids like water, alcohol, honey or milk. The use of medicinal plants is so wide spread across the world that the World health Organization estimates 80% of the population of the world engages in the use of herbal medicines [1]. Peptic Ulcer Disease (PUD) is a serious gastrointestinal disorder that requires a well targeted therapeutic strategy. A number of drugs including proton pump inhibitors and H_2 receptor antagonists are available for the treatment of peptic ulcer, but clinical evaluation of these drugs has shown incidence of relapses, side effects, and drug interactions. This has been the rationale for the development of new anti-ulcer drugs and the search for novel molecules has been extended to herbal drugs that offer better protection and decreased relapse. Drugs of plant origin are gaining popularity and are being investigated for a number of disorders, including peptic ulcer [2, 3]. Therefore, present study was designed to investigate the gastroprotective effects of methanol extract of dried leaves of *Artocarpus heterophyllus* Lam. on indomethacin-induced gastric ulceration. Leaves of *Artocarpus heterophyllus* Lam. (Jackfruit) is a species of tree of the mulberry family (Moraceae) is traditionally used as in convulsions [4]. It is native to Western Ghats of India, Malaysia and also found in central and eastern Africa, South-eastern Asia, Florida, Brazil, Australia and many Pacific Islands [5, 6]. The plant was reported to possess Anti-allergic [7],

antibacterial [8], anti-inflammatory [9], anti-diabetic [10], antioxidant [11, 12], antifungal [13] and immunomodulatory properties [14] which are useful in fever, boils, wounds, skin diseases, convulsions, diuretic, constipation, ophthalmic disorders and snake bite etc [15].

The tree is also known for its durable timber and possesses anti-termite, and melanin biosynthesis inhibitor properties [16, 17]. The plant also contains free suger (sucrose), fatty acids, ellagic acid and some essential Amino acids like Arginine, Cystine, Histidine, Leucine, Lysine, Metheonine, Theonine, Tryptophan etc [18]. A decoction (Kadha) administered orally before breakfast has been advocated by local traditional medical practitioners. Indomethacin is a potent prostaglandin (PG) biosynthesis inhibitor, and inhibition of PG synthesis by indomethacin coincides with the earlier stages of damage to the cell membranes of mucosal, parietal and endothelial cells. It has been reported that gastric acid secretion is involved in the formation of indomethacin-induced mucosal lesions. Traditionally the ash of *Artocarpus heterophyllus* Lam. (Jackfruit) leaves is used in the treatment of ulcers so we also expected that the leaves of the above plant also possess the anti-ulcer activities & therefore carried out the screening for the same [19].

MATERIALS AND METHODS

Plant material and animals

The plant material was collected from the local market from Lucknow and authenticated by taxonomic division of N.B.R.I. Lucknow India and a voucher specimen was deposited for future references (Ref.No.NBRI/CIF/96/2009). Swiss Albino mice and Albino rats of either sex each weighing between 20-25grams and 150-175grams respectively were selected for anti-ulcer activity. Both the strains were preserved under good hygienic condition in the departmental animal house. During the period of acclimatization animals were examined properly for infection, metabolic disorder, and protected from hurting each other by aggressive behavior. Six animals were kept together. Animals were housed under standard condition of temperature (23 ± 1^0C) and relative humidity (55±10%), 12hour light/12hr dark cycle and given water, *ad libitium*.

Preparation of Plant extracts

The dried leaves of *Artocarpus heterophyllus* Lam. (250gm) was reduced to powder (60 mesh) and then extracted with 70% methanol by using soxhlet extractor. The methanolic extract was filtered through cotton plug; the solvent was distilled off by rotary evaporator and finally reduced to dryness on desiccator (with $CaCl_2$) and used for all experimental studies.

Drugs

The methanolic extract of leaves of *Artocarpus heterophyllus* Lam. was suspended in distilled water with 1% Tween 80 solution. In this study (Anti ulcer activity) indomethacin I.P. (Ranbaxy Chemical and Pharmaceutical Ltd) was used to produce ulcer in rat whereas Ranitidine (Ranbaxy Chemical and Pharmaceutical Ltd.) was used as standard to determine anti ulcer activity.

Acute toxicity studies

Alcoholic extracts were administered orally in the dose ranging of 200-5000mg/kg body weight to ten groups of mice. There was no mortality in any of the groups. Mice, which received any of the extract in doses above 5000mg/kg body weight exhibited ptosis (dropping of upper eyelids) and were found to be lethargic. $1/10^{th}$ of the maximum dose of the extract tested for acute toxicity was selected for evaluation of anti-ulcer activity i.e. 500mg/kg b.w. The 'Up and Down' or 'Staircase' method was adopted, and appropriate dose of methanolic extract was administered. Two mice were orally dosed, say 250mg/kg and observed for a period of 24hours for any mortality. The subsequent doses were then increased by a factor 1.5, if the dose was tolerated, or decreased by factors 0.7 if it was lethal. The maximum non-lethal and the minimum lethal dose were determined using only about 10 mice. Once the approximate LD_{50} or the range between the maximum non-lethal and minimum lethal dose was found, a final and more reliable LD_{50} assay was planed using at least 3 or 4 dose levels within this range with more number of animals in each group. LD_{50} was expressed in term of mg/kg. In addition, source of animal, sex, age, body weight, oral time and solvent, and presence and absence of any immediate reaction were also recorded for further references [20]. The maximum non-lethal dose was found to be 5000mg / kg body weight, hence $1/10^{th}$ of which was taken as effective dose (500mg / kg body weight) for alcoholic extract of leaves of *Artocarpus heterophyllus* Lam. The total alcoholic extract of leaves of *Artocarpus heterophyllus* Lam. was tested for toxicity in mice up to the dose 5000mg / kg body weight for one week. There was no Mortality of animals whatsoever. Thus, the total alcoholic extract of

leaves of *Artocarpus heterophyllus* Lam. as found to be safe and non-lethal at this higher dose.

Anti-ulcer activity methods

Indomethacin induced gastric ulcer

Albino rats of either sex weighing between 150-175gm were housed in group of six in standard laboratory housing condition prior to experimentation. They were usually fasted for a period of 24-39 hours, allowing free excess to drinking water *ad libitium* prior to drug administration orally. Animals were divided into four groups of six animals each. Group I was a vehicle control which received normal saline (2ml/kg body weight). Group II was diseased control which received indomethacin in a dose of 20mg/kg body weight (4mg/ml dissolved in 0.1% Tween 80 solution) and the vehicle as well. Group III received methanolic extract of leaves of *Artocarpus heterophyllus* Lam. (500mg / kg body weight) and the vehicle as well. Group IV received standard drug (Ranitidine, 20mg/kg body weight) and the vehicle as well. After 30 min the indomethacin was administered intraperitoneally at a dose of 20 mg/kg body weight *p.o.* After four hours under light ether anesthesia, abdomen was open by small middle incision below the Xiphiod process, pyloric portion of the stomach is slight lifted out and legated avoiding traction of pylorus or damaged to its blood supply. Then the stomach was replaced carefully and abdominal wall closed by interrupted sutures. The rats were deprived of both food and water during the post- operative period and were sacrificed at the end of 19hours. Stomach is dissected out and content of the stomach were drained into measuring cylinder and this was subjected to pH analysis of pH and concentration of acid in gastric juice. The gastric contents were centrifuged at 1000rpm for 10 min, 1ml of supernatant was diluted with 1ml of distilled water, titrated against 0.1N sodium hydroxide using Topfer's reagent (as an indicator) till the solution turned to orange colour. The volume of sodium hydroxide required (Corr.) responds to the total acidity. The stomach was cut open along the grater curvature and the inner surface is examined for ulceration microscopically. Usually circular lesions were observed [21, 22].

Statistical analysis

The results are expressed as Mean ± SEM and statistical significance was measured by means of one way ANOVA followed by Newman-Keuls Test [23]. Significance of difference was accepted at $P< 0.05$.

RESULTS

1) Estimation of pH of Gastric contents

In control animals, without any drug treatment, the mean pH was found to be 2.9 ± 0.38. The pH in Indomethacin control group animal is 2.3 ± 0.59. The pH is slightly increased but it is significant compared to the control group. The methanolic extract of leaves of *Artocarpus heterophyllus* Lam. was tested against Indomethacin induced changes in pH. Ranitidine, marketed drug used in peptic ulcer, was taken as standard for comparison. Methanolic extract of leaves of *Artocarpus heterophyllus* Lam. significantly increased the pH to 3.36 ± 0.092 ($P<0.01$). Ranitidine, the standard drug increased the pH to 3.46± 0.125 ($P<0.01$).

2) Estimation of concentration of acid in gastric content (m.eq/lit)

Total gastric acidity was significantly increased with Indomethacin treatment (0.18±0.025m.eq/lit) when compared to control (0.14± 0.005m.eq/lit). Methanolic extract of *Artocarpus heterophyllus* Lam. significantly decreased the acidity induced by Indomethacin. However, Ranitidine (standard drug) was found to be more potent than the methnolic extract of leaves of *Artocarpus heterophyllus* Lam.

3) Gastric ulcer scoring in Indomethacin induced ulcer model

Administration of Indomethacin resulted in the production of gastric lesions. The mean gastric ulcer score in group II was found to be 5.83±0.872 and statstically significant ($P<0.001$) than the control. In protecting the Indomethacin-induced ulcer. The alcoholic extract of leaves of *Artocarpus heterophyllus* Lam. (1.83±0.307) was found to be statistically significant in reducing gastric ulcer score. However Ranitidine (Ulcer score) was to be more potent ($P<0.001$) than the leaves extract ($P< 0.001$). In case of indomethacin induced ulceration, the methanolic extract of *Artocarpus heterophyllus* Lam. reduced the ulcer score from 5.83±0.872 (in indomethacin treated) to 1.83±0.307, $P<0.01$.

DISCUSSION

The etiology and pathogenesis of ulcers in the most part remains unknown and even controversial [24, 25]. But it is quite well known that ulcers in the gastrointestinal tract, which could be gastric or duodenal, come about because of injury to the gastrointestinal walls. The injury could arise as a result of many factors. It is believed that the pathogenesis depends mainly on the interplay of two main factors. These include aggressive factors such as acid, bicarbonate, pepsin and defensive mechanisms involving the mucosal barrier, mucus and mucus turn over as well as blood supply [26]. The alcoholic extract of leaves of of *Artocarpus heterophyllus* Lam. at the dose of 500mg /kg body weight showed statistically significant & considerable anti-ulcer activities. However, the standard drugs were found to be more effective in both cases. The leaves of the plant have shown statistically significant and considerable anti-ulcer activities comparable to the standard drugs. Ulcers are caused due to imbalance between aggressive and defensive factors of the gastric mucosa. Pepsin and gastric acid make up the offensive factors whose proteolytic effect is buffered by mucin secretion, mucosal glycoprotein, cell shedding, cell proliferation and prostaglandins [27, 28]. The adrenergic system is involved in gastric secretion [29]. It has been shown in the gastrointestinal tract that activation of presynaptic α_{2}- adrenoceptors located on the vagus nerve inhibit gastric acid secretion [30]. The family Moraceae consists of about 40 genera and some 1,000 species of deciduous or evergreen trees and shrubs, distributed worldwide mostly in tropical and subtropical regions. This family contributes a number of medicinal plants used in traditional system of medicine for example; *Ficus insipida*, *Castilla elastic*, *Brosimum lactescens and Trophis involucrata* etc. are known to possess a number of therapeutic properties [31]. The literature on chemical investigation and pharmacological actions of the plants belonging to this family is very exhaustive. Surprisingly, the literature survey on Jackfruit revealed that, the chemical or pharmacological investigation is not as exhaustive as those of other genus of this family. Though there are a few reports of chemical and pharmacological investigations of *Artocarpus heterophyllus* Lam. but pharmacological work has not been reported for the leaves of *Artocarpus heterophyllus* Lam. in the literature. The leaves of *Artocarpus heterophyllus* Lam. contain Flavonoids, Glycosides, Tannins, Carbohydrates, Triterpenoids and Amino acids as its chemical constituents. Tentatively it can be said that flavonoids/coumarins are the active constituents in the leaves and are responsible for its pharmacological actions. The present study, confirms that leaves of *Artocarpus heterophyllus* Lam. has anti-ulcer activity. Further it is also possible that the anti-ulcer effect of the *Artocarpus heterophyllus* Lam. may be due to their effects on various other mucosal defensive factors like prostaglandin accumulation, bicarbonate balance, mucosal glycoprotein, phospholipid layer integrity, tight junctions, cell restitution, cell proliferation and mucosal blood flow. It also further necessitates further chemical and pharmacological studies in future.

Table1- Effect of Leaves of *Artocarpus heterophyllus* Lam. on Gastric Secretion

Groups	Treatments	Dose (as per body weight)	pH of gastric contents	Concentration of acid in gastric content (Meq/Lit)	Gastric ulcer score
I	Control (Normal saline)	2ml /kg	2.9 ± 0.38	0.14±0.005	0.6±0.421
II	Indomethacin control	20mg /kg	2.3±0.025	0.18±0.025	5.83±0.872
III	Indomethacin Alcoholic extract	500mg / kg	3.36±0.092**	0.08±0.006**	1.83±0.307***
IV	Indomethacin & Ranitidine	20mg / kg	3.46±0.125**	0.12±0.009	0.66±0.333***

Parameters and on Ulcer Score

The values are expressed as Mean±SEM (n=6), statistically significant *P<0.05, **P<0.01, ***P<0.001. Data were analysed using one way ANOVA followed by Newman-Keuls Multiple Comparison Test.

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